Docket No. 44657-AAA-PCT-US/JPW/GJG/CS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Appellant : Joseph R. Berger

Serial No.: 10/052,961 Group Art Unit: 1617

Filed : January 18, 2002 Examiner: S. Wang

Title : A METHOD FOR AMELIORATING MUSCLE WEAKNESS/WASTING IN A PATIENT INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS-TYPE 1

30 Rockefeller Plaza
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APPEAL BRIEF

This appeal is taken from the Examiner's rejection of claims 88-105 in the Office Action issued March 30, 2011 in connection with the above-identified application. The required fee for filing an Appeal Brief in support of an appeal under 37 C.F.R. §41.20(b)(2) for a small entity is TWO HUNDRED AND SEVENTY DOLLARS ($270.00), and authorization is hereby given to charge this amount to Deposit Account No. 03-3125.

Appellant filed a Notice of Appeal on June 30, 2011, which was received by the U.S. Patent and Trademark Office on June 30, 2011. Accordingly, based on the June 30, 2011 receipt date of the Notice of Appeal, appellant's brief on appeal is due August 30, 2011. Accordingly, this Appeal Brief is being timely filed.

No fee, other than the $270.00 fee, for which the

authorization to charge Deposit Account No. 03-3125 has been given above, is deemed necessary in connection with the filing of this Appeal Brief. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

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1. REAL PARTY IN INTEREST

The owner of the subject application at the time of filing this brief is Savient Pharmaceuticals, Inc., a corporation organized under the laws of Delaware and having a place of business at One Tower Center Boulevard, 14th Floor, East Brunswick, New Jersey 08816, the assignee of record of the above-identified patent application by virtue of a name change from Bio-Technology General Corp., recorded on January 16, 2004 with the U.S. Patent and Trademark Office at Reel 014871 Frames 0808-0813, a copy of which is attached hereto as **Appendix B.1**.

Bio-Technology General Corp. was the assignee of record of the above-identified patent application by virtue of a merger and name change from BTG Pharmaceuticals Corp., recorded on March 8, 2004 with the U.S. Patent and Trademark Office at Reel 015043, Frames 0366-0369, a copy of which is attached hereto as **Appendix B.2**.

BTG Pharmaceuticals Corp. was the assignee of record of the above-identified patent application by virtue of an assignment from the inventor, Joseph R. Berger, recorded on June 20, 1994 with the U.S. Patent and Trademark Office at Reel 007697 Frames 0179-0181, a copy of which is attached hereto as **Appendix B.3**.

2. RELATED APPEALS AND INTERFERENCES

U.S. Serial No. 10/052,961, filed January 18, 2002, is a continuation of U.S. Serial No. 09/469,817, filed December 22, 1999, now U.S. Patent No. 6,670,351, issued December 30, 2003, which is a continuation of U.S. Serial No. 08/244,988, filed June 22, 1995, now U.S. Patent No. 6,090,799, issued July 18, 2000, which is a §371 national stage application of PCT/US1993/010063, filed October 20, 1993, which is a continuation of U.S. Serial No. 07/963,469, filed October 20, 1992, now abandoned.

U.S. Patent Nos. 6,670,351 and 6,090,799 were involved in Savient Pharmaceuticals, Inc. v. Sandoz, Inc. and Upshur-Smith Laboratories, Inc., Case No. 06-CV-5782 (PGS), U.S. District Court For The District of New Jersey. The District Court issued on December 8, 2006 an Order vacating temporary restraints, a copy of which is attached hereto as **Appendix C.1**.

A Notice of Appeal to the U.S. Court of Appeals of the Federal Circuit was filed by Savient Pharmaceuticals, Inc. on December 12, 2006 and was assigned Appeal No. 2007-1081. By parties' agreement, the Federal Circuit issued a January 25, 2007 Order dismissing the appeal, a copy of which is attached hereto as **Appendix C.2**.

The District Court proceeding was subsequently terminated when parties stipulated to dismiss claims and counterclaims, copies of Stipulations and Orders are attached hereto as **Appendix C.3 and C.4**.

3. STATUS OF CLAIMS

Claims 88-106 as reproduced in **Claims Appendix** are pending in the subject application. Claims 88-105 have been twice rejected and are being appealed. Claim 106 has been deemed withdrawn.

4. STATUS OF AMENDMENTS

Claims 88-105 were rejected and claim 106 was deemed withdrawn in a Final Office Action issued March 26, 2010 in connection with the above-identified application. Appellant filed a Notice of Appeal and a Petition for Three-Month Extension of Time on September 27, 2010. Appellant filed on December 22, 2010 a Communication In Response to March 26, 2010 Office Action As The Required Submission Under 37 C.F.R. 1.114(C) For The Accompany Request For Continued Examination and Petition For One-Month Extension of Time. Appellant did not add, cancel, or amend any claim in the December 22, 2010 Communication. Claims 88-105 were rejected for a second time and claim 106 was deemed withdrawn in an Office Action issued March 30, 2011 in connection with the above-identified application. Appellant filed a Notice of Appeal on June 30, 2011.

Accordingly, appellant has not filed any amendment subsequent to the final rejection of claims 88-105 in the March 26, 2010 Final Office Action.

5. SUMMARY OF THE CLAIMED SUBJECT MATTTER

Independent claim 88 is directed to a solid pharmaceutical composition in unit dosage form comprising a pharmaceutically acceptable carrier and 10 mg of oxandrolone per unit dosage form.

Claim 88	Specification
A solid pharmaceutical composition in unit dosage form	Page 5, lines 19-22; and page 7, lines 21-27.
comprising a pharmaceutically acceptable carrier and	Page 5, lines 20-21; and page 7, lines 24-27.
10 mg of oxandrolone per unit dosage form.	Page 4, lines 3-5.

Independent claim 94 is directed to a tablet comprising a pharmaceutically acceptable carrier and 10 mg of oxandrolone per tablet.

Claim 94	Specification
A tablet	Page 6, line 35 to page 7, line 2; and page 7, line 9.
comprising a pharmaceutically acceptable carrier and	Page 5, lines 20-21; and page 7, lines 24-27.
10 mg of oxandrolone per tablet.	Page 4, lines 3-5.

Independent claim 100 is directed to a tablet comprising corn starch, hydrous lactose, hydroxypropyl methylcellulose, magnesium stearate, and 10 mg of oxandrolone per tablet.

Claim 100	Specification
A tablet	Page 6, line 35 to page 7, line 2; and page 7, line 9.
comprising corn starch, hydrous lactose, hydroxypropyl methylcellulose, magnesium	Page 7, lines 13-20.

stearate, and	
10 mg of oxandrolone per tablet.	Page 4, lines 3-5.

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

There are two specific grounds of rejection to be reviewed.

Claims 89-105 have been rejected under 35 U.S.C. §112 as allegedly containing subject matter not described in the specification so as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In addition, claims 88-105 have been rejected under 35 U.S.C. §103(a) as allegedly obvious over Metcalf et al. (1965) *Metabolism* 14(1):59-66, in view of ANAVAR® Physician's Product Brochure, and Babu et al. (U.S. Patent No. 5,073,380), and "further in view of applicant's admission at page 7".

7. ARGUMENT

7.1 REJECTION UNDER 35 U.S.C. §112 (WRITTEN DESCRIPTION)

The Examiner rejected pending claims 89-105 as allegedly containing subject matter not described in the specification so as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Examiner stated on page 2 of the March 30, 2011 Office Action that the application has a "single example of tablet which is composed of 2.5 mg of oxandrolone, and specific amount of corn starch, hydrous lactose, hydroxypropyl methylcellulose, and magnesium stearate." The Examiner acknowledged on pages 2-3 of the March 30, 2011 Office Action that the application "merely mentions 10-milligram dose referring to a prior study, and no dosage form is disclosed, nor any further information as to the carrier and particular forms." The Examiner however asserted on page 3 of the March 30, 2011 Office Action that "it is not clear whether the 10 mg dose is administered in single unit dosage form, or in multiple dosage forms." The Examiner also asserted that "the application, as originally filed, lacks support of a solid unit dosage form, or tablet comprising 10 mg of oxandrolone, and one [or] more of corn starch, hydrous lactose, hydroxypropyl methylcellulose, and stearate, nor to the particular amounts of the carriers."

Appellant respectfully submits that the specification of the subject application does reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the claimed.

I. Legal Standard For Written Description Requirement

The written description requirement is provided in 35 U.S.C. §112, which states:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

A specification fulfills the written description requirement when it "reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc), a copy of which is attached hereto as **Appendix B.4**. There is no requirement that the application describes the claimed subject matter in exactly the same terms as used in the claims. *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000), a copy of which is attached hereto as **Appendix B.5.**

II. Specification Reasonably Conveys The Claimed Invention

Appellant respectfully submits the specification does reasonably convey to one skilled in the art that the inventor had possession of the claimed invention as of the filing date. Specifically, support for the claimed invention may be found in at least the following sections of the specification:

> "Oxandrolone disposition and metabolism in man has been studied following oral administration of a 10 milligram dose. The study indicated that oxandrolone was rapidly and completely absorbed, yielding a mean peak plasma concentration of 417 micrograms of oxandrolone per milliliter at 66 minutes. The plasma

concentration of oxandrolone declined in a biphasic manner with a distribution half-life of approximately 30 minutes and an elimination half-life of 9.4 hours. Protein binding of oxandrolone was observed to be extensive." (Page 4, lines 3-13, emphasis added)

"For purposes of administration in accordance with this invention, the active ingredient oxandrolone is combined with solid or liquid pharmaceutical carriers and formulated in unit dosage form using pharmacologically acceptable excipients, or dissolved or suspended in physiologically acceptable solvents or liquid vehicles for oral, percutaneous, or topical administration." (Page 5, lines 19-26, emphasis added)

"The overall daily dose of oxandrolone to provide a therapeutically effective amount in accordance with the method of this invention can be as low as about 2.5 milligrams and as high as about 20 milligrams, depending upon the patient's response and the mode of administration." (Page 5, lines 27-32, emphasis added)

"The patient's daily dose of the active ingredient preferably is in the range of about 7.5 milligrams, but may exceed 20 milligrams based on clinical response. This daily dose can be given in tablet form as a single dose, or as plural divided doses, preferably 2 to 3 divided doses." (Page 6, line 32 - page 7, line 2, emphasis added)

a) 10 mg Unit Dose Of Oxandrolone

The specification expressly discloses that oxandrolone may be administered in a 10 mg unit dose, specifically as a tablet. The specification expressly describes that a dose from 2.5 mg, or preferably 7.5 mg, to 20 mg of oxandrolone may be administered "in tablet form as a single dose." The specification also expressly describes that a 10 mg dose of oxandrolone may be administered.

A person of ordinary skill in the art reading the dosages described in the specification together with the specification's disclosure that the dosages can be in single dose form, would instantly understand that the appellant had possession of 10 mg unit dose of oxandrolone as of the filing date.

b) Composition Comprising Recited Carriers

To the extent that claims recite a composition, or a tablet, comprising pharmaceutically acceptable carriers, the Examiner acknowledged on page 2 of the March 30, 2011 Office Action that certain oxandrolone tablet compositions were known in the art. The specification also expressly discloses that an oxandrolone tablet may contain "corn starch, lactose NF (hydrous), hydroxypropyl methylcellulose, and magnesium stearate". (Page 7, lines 16-19)

MPEP 2163(II)(A)(1) provides that "absence of definitions or details for well-established terms or procedures should not be the basis for a rejection under 35 U.S.C. 112, para. 1, for lack of adequate written description". MPEP 2163(II)(A)(2) explains that "there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement".

Appellant respectfully submits that tablet formulation was well established art at the time of filing. Therefore, the notion that a skilled artisan, for example a pharmaceutical scientist, would somehow fail to understand that a 10 mg oxandrolone unit dosage form can contain the pharmaceutically acceptable carriers listed in the specification is not

tenable.

In view of the support in the specification and the legal standard for complying with the written description requirement as discussed above, it is not tenable to maintain that the specification does not reasonably convey to one skilled in the art the claimed "tablet comprising corn starch, hydrous lactose, hydroxypropyl methylcellulose, magnesium stearate, and 10 mg of oxandrolone per tablet". Appellant therefore requests the Board to reverse this ground of rejection.

7.2 REJECTION UNDER 35 U.S.C. §103(A)

The Examiner also rejected claims 88-105 under 35 U.S.C. §103(a) as allegedly obvious over Metcalf et al. (1965) *Metabolism* 14(1):59-66, in view of ANAVAR® Physician's Product Brochure, and Babu et al. (U.S. Patent No. 5,073,380), and "further in view of applicant's admission at page 7".

The Examiner asserted that Metcalf et al. teach a method of using oxandrolone for nitrogen retention wherein the daily amounts of oxandrolone are from 5 mg, 10 mg, 20 mg, and up to 150 mg. The Examiner acknowledged that according to Metcalf et al. the optimal oxandrolone dosage is about 25 mg or 30 mg a day. The Examiner also acknowledged that Metcalf et al. do not teach a unit dosage form comprising 10 mg of oxandrolone and the particular pharmaceutical excipients.

The Examiner stated that ANAVAR® Physician's Product Brochure discloses an oxandrolone tablet, wherein the inactive ingredients include corn starch, lactose, magnesium stearate and methylcellulose. The Examiner asserted that ANAVAR® teaches that daily dosage of oxandrolone may be up to 20

mg/day.

The Examiner asserted that Babu et al. disclose that hydroxypropyl methylcellulose is a typical excipient for tablet formulation. The Examiner also asserted that applicant admits that tablet formulation comprising oxandrolone, corn starch, hydrous lactose, hydroxypropyl methylcellulose and magnesium stearate is known in the art.

Appellant respectfully submits that the cited prior art references do not teach the claimed invention, even under the Examiner's interpretation.

I. *Appellant was first to identify the problem to which a 10 mg unit dosage form is a solution*

a) Appellant was the first to identify oxandrolone as a treatment for AIDS symptoms

Prior to appellant's invention as disclosed in the present application, it was not known that oxandrolone could be used to treat certain symptoms of AIDS and side effects of AIDS therapy, such as HIV-associated myopathy, muscle weakness, and muscle wasting. None of the cited references teaches such treatment using oxandrolone.

b) AIDS patients have high pill burdens due to polypharmacy treatments, which results in patient compliance issues unique to such patients

AIDS patients are often treated in clinic with multiple tablets simultaneously to counter various symptoms of AIDS and side effects of the AIDS treatments. This treatment regime results in art-recognized pill burden issues for AIDS patients and HIV-positive patients leading to compliance and adherence

problems (e.g. see **Appendix B.6** at page 281, "Pill Burden Key To Doing Well"; and **Appendix B.7** at page 136 "Daily Pill Burden and Adherence").

c) Prior to appellant's identification of oxandrolone as a treatment for AIDS symptoms, there was no motivation to make unit dose forms of oxandrolone greater than the 2.5 mg unit dose form already available

Oxandrolone had been manufactured only in a 2.5 mg unit dose since the early 1960s (e.g. see Anavar® Physician's Product Brochure). Prior to appellant's discovery of the use of oxandrolone in treating AIDS patients, and thus prior to identification of a specific pill burden issue with respect to oxandrolone, there existed no motivation to make a unit dose form comprising 10 mg oxandrolone. Nothing in the cited prior art direct one to select a 10 mg unit dosage form, and the Examiner fails to cite evidence to the contrary. However, *after* identification of oxandrolone as a treatment for AIDS symptoms consideration of the problem of pill burden arose. This previously unidentified problem is addressed by appellant's claimed unit dose form containing 10 mg oxandrolone.

d) The claim invention is nonobvious since pill burden and patient compliance issues were previously unknown

Case law guides that a claim is nonobvious if the problem which had suggested use of the claimed invention was previously unknown. For example, *In re Omeprazole Patent Litigation*, the Federal Circuit affirmed district court's decision that a pharmaceutical composition comprising omeprazole and an inert subcoating is not obvious since prior art references did not "disclose or suggest a negative interaction between the drug core and the enteric coating", where the later claimed inert subcoating is a solution to

prevent such negative interaction. (536 F.3d 1361, 1379, a copy of which is attached hereto as **Appendix B.8**)

Similarly, the prior art references cited by the Examiner do not disclose or suggest a problem, e.g. pill burden and patient compliance issues discussed above, to which a 10 mg unit dosage form of oxandrolone is a solution. Consequently, there was no motivation to make a unit dose form comprising 10 mg oxandrolone as of the effective filing date of the subject application. Therefore, the invention as claimed is not obvious over the cited prior art.

II. The Cited References Do Not Teach Or Suggest Appellant's Claimed Invention

In addition to the failure of the prior art to identify the problem to which a 10 mg unit dosage form of oxandrolone is a solution, the cited references do not teach or suggest appellant's claimed invention.

Specifically, Metcalf et al. teach that the optimal combined daily amount is 25-30 mg per day (see Metcalf et al. page 63). Metcalf et al. also report "variable response at low dose levels" (*Id.* at page 60). In addition, Metcalf et al. state that "[t]he drug was given orally each morning" (*Id.*, second full paragraph). In view of the teaching to give 25-30 mg orally each morning, and the variable response at lower dosages, a person of ordinary skill in the art would have no reason to even consider producing a 10 mg unit dosage form of oxandrolone.

Appellant's position is supported by a previously submitted Declaration Under 37 C.F.R. 1.132 of Faith Ottery, M.D., Ph.D., FACN, (the "Declaration", submitted as Exhibit 1 to a

May 15, 2008 Communication in Response to November 15, 2007 Office Action, a courtesy copy of the Declaration is attached hereto as **Appendix B.9**).

In the Declaration, Dr. Ottery explained that the nitrogen-retention ratio, as proposed by Metcalf et al., has not been validated as a standard to be indicative of muscle mass change generally, or in HIV patients specifically. Nitrogen retention as used by Metcalf et al. is a complex interplay of a number of variables and is not necessarily indicative of muscle mass or of muscle strength. It is therefore unpredictable based on Metcalf et al. whether the "optimum" dose for maximum "nitrogen sparing" with oxandrolone of 25-30 mg per day would be optimum dose for ameliorating muscle weakeness or wasting in a patient, such as an HIV patient. See the Declaration, paragraph 5.

Dr. Ottery also explained in the Declaration that the cited references can only be reasonably interpreted to suggest a 25-30 mg unit dosage form for oxandrolone. Moreover, in view of pill-burden and patient-compliance issues, the cited references did not provide any motivation to make a 10 mg unit dose form of oxandrolone instead of a 25-30 mg unit dose form, or yet some other dose form. See the Declaration, paragraphs 6-8.

Furthermore, Dr. Ottery provided in her Declaration additional prior art reference which shows administration of a single 20 mg oxandrolone tablet per day to HIV patients was statistically similar to placebo results in treating weight loss in HIV patients. See the Declaration, paragraph 9.

The rejection of record provides no rationale which is

supported by prior art evidence to maintain contrary position.

Accordingly, appellant respectfully submits that the rejection of record is fatally defective.

III. The Examiner has used impermissible hindsight to specifically select a unit dose form comprising 10 mg oxandrolone

Finally, were hindsight appropriate, it would have been possible to make up a convenient regimen to arrive at the claimed invention. However, as the rejection stands on appeal there is no rationale of record which based on the cited art for a 10 mg unit dose form. The only recitation of a 10 mg dose is not as a unit dose form (see Metcalf et al.) More importantly, Metcalf et al. teach that the 10 mg dose is not effective (see left hand column of Abstract and page 60 of Metcalf et al.) Thus, the 10 mg unit dose form is being "created" by the Examiner without any rationale based on prior art; the art cited by the Examiner in fact teaches away from a 10 mg unit dose form.

For this and other reasons above, the rejection is improper.

7.3 CONCLUSION

For the foregoing reasons, appellant respectfully submits that the Examiner's rejections of claims 88-105 are erroneous, and respectfully submit that the rejections of these claims should be reversed.

Respectfully submitted,

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